January 1993. By that time, the invention embodied in the claims of the subject application had been reduced to practice prior to the publication of Rice on July 1993. Thus, the subject application was filed less than one year prior to the publication of Rice. Further, the invention was reduced to practice at least by January 19, 1993 when the Rice article was received by the Journal of Bateriology. Indeed, it was accepted on 27 April 1993, another date earlier than the July 1993 date of publication.

Accordingly, the article by Rice is not prior art.

The combination of Xiong et al and Hsu et al with either one of the two Inouye patent relied upon patents do not teach or suggest the subject matter claimed.

Claim 13 the broadest claim in this patent application; recites a bacterial reverse transcriptase that synthesizes msDNA and is necessary for the synthesis of msDNA *in vivo*. Dependent claims further define the RT by reciting the presence in the order specified of four specific conserved regions within the various bacterial RTs.

The Examiner rejects all claims based on two earlier patents from Inouye, 5,320,958 and 5, 434,070 in combination with Rice et al., Xiong et al. and Hsu et al. The Examiner states that the patents teach the isolation of RTs from *E. coli* and *M. xanthus*. Xiong et al. show the amino acid sequences of 82 RTs from viruses, bacteria, plants and animals, and Hsu et al. show the similarity of RTs of *M. xanthus* and *S. aurantica*. The Examiner concludes that one skilled in the art could use the teaching of the two patents to isolate RTs from any bacterial source, and is motivated to do so by the teachings of the secondary references that show RTs exist in bacteria other than *E. coli* and *M. xanthus*.

However, Rice, who shows the presence of retrons and RTs in diverse groups of bacteria is not prior art as discussed above. There is no teaching or suggestion in the other references to suggest that retrons or RTs exist is any bacteria other than E. coli or Myxobacteria (*M. xanthus* and *S. aurantica*). The Hsu et al. and Xiong et al. references also show only RTs derived from this limited group of bacteria. Indeed, the teaching in the present application is the first to show that retrons and RTs exist in a wide variety of diverse prokaryotes. Without the teaching of the present invention, there is no guidance or motivation to one skilled in the art to examine other

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genera or species of bacteria for retrons or RTs. To rely on the present application, would be hindsight, which is not permissible. Indeed, even among strains of *E. coli* and Myxobacteria,* only a small percentage are known to express RT (typically from 10-20%). See Hsu, page 2385.

It is clear that, in the absence of the teaching of the present invention, the incidence of RTs in other bacteria would be expected to be rare and would require and be merely an invitation to experimentation to find the particular prokaryotes that have the features of claim 13, 17 and of the other claims.

The Examiner also states that the amino acid sequences of various viral and eukaryotic RTs presented by Xiong et al. would provide direct motivation and guidance to isolate RTs from other bacteria. The applicants respectfully disagree since the RTs of the invention possess an activity, i.e., the synthesis of msDNAs that is not present in eukaryotic RTs. None of the eukaryotic RTs synthesizes msDNA in vivo, nor are they essential for the generation of msDNA within the cell. However, that is a specific property of the RTs of the present invention and that property is specifically recited in claim 13 and claims dependent thereon. Thus, the prokaryotic RTs of the present invention are not taught or suggested by Xiong et al and/or Hsu et al. Note that the only prokaryotic RTs included in the Xiong et al are from *E. coli* and Myxobacteria. The recitation and comparison of different amino acid sequences of RTs provides no motivation to one skilled in the art to search for RTs from other bacteria. Indeed, the specific structural properties, i.e., the four conserved amino acid regions of the bacterial RTs of the present invention are not conserved in their entirety in the RTs of Xiong et al. Within these four regions, variation in sequence is common among the RTs of Xiong et al. There is no guidance as to which specific sequence is optimally homologous to other bacterial RTs. Taken in combination with the teaching of the prior art that the incidence of RTs in other bacteria is very low, one skilled in the art would not be motivated to search for new bacterial RT sequences since this would appear at the outset to be find a fruitless search, certainly not with an expectation of success. More likely, such search if attempted would lead away from the invention.

Claim 17 which has been added calls for the four identified amino acid sequences and residues in the order recited starting from the N– to the C- terminus. There is no teaching or suggestion whatever in the references relied upon that teaches or suggests such RT's.

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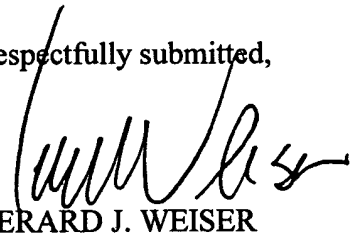
For the above reasons, it is submitted that the prior art relied upon does not teach or suggest the subject matter claimed. Favorably review and an early allowance are respectfully solicited.

Should the Examiner see any remaining issues, he is respectfully requested to call the undersigned at the telephone number shown below.

Respectfully submitted,



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